Computational Studies on C–C and C–N Coupling Reactions

Summary of the PhD Dissertation

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1 Introduction

The ongoing and successful development of the theoretical chemical tools and the available hardwer and software environment enabled to obtain deeper insights into the mechanism of organic chemical reactions. The PhD thesis addresses the exploration of reaction mechanisms of current organic chemical transformations in strong collaboration with experimental partners. The applications summarized in the thesis all focus on coupling reactions, i.e., C–C and C–N bond formations. Three of them scrutinize coupling reactions where the coupling was achieved by iodonium salts, while the last project is a computational exploration of intramolecular rearrangements. My contributions were the explore plausible reaction routes and to identify the most likely reaction paths. In addition, whenever it was possible, a further step has been taken to give predictions regarding the reactivities, the scope or the outcome of the reactions.

2 Methods

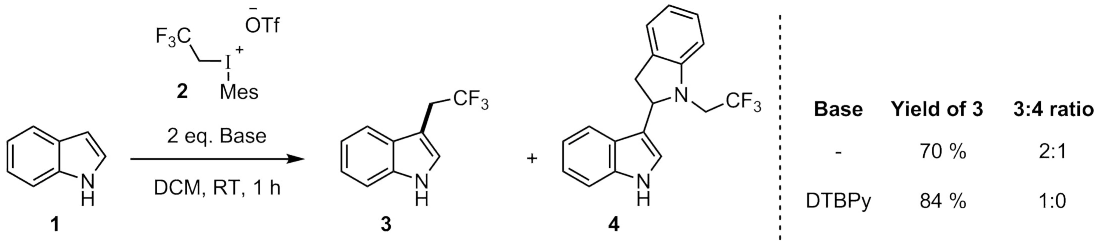
In order to identify reaction paths, we located the corresponding minima and the connecting transition states along the path on the ground-state potential energy surface. The solvent–corrected Gibbs free energies of the alternative reaction paths have been compared. To this end, we have applied density functional methods: in the case of metallic systems the M06 hybrid *meta*-GGA functional was used, whereas in the other cases the ωB97X-D range-separated hybrid functional has been used. The geometry optimizations and thermodynamic corrections were calculated on double-ζ basis sets. Iodine and palladium have been treated with LANL2 pseudopotentials and the LANL2DZ basis set with additional set of polarization and diffuse functions taken from the aug-cc-pVDZ-PP basis set. All other elements have been optimized on the 6-31+G* basis set. To obtain the Gibbs free energies, the ideal gas – rigid rotor – harmonic oscillator approximation was applied. The solvent-corrected Gibbs free energies were determined using the SMD polarizable continuum model on triple-ζ basis sets: LANL2TZ(f) for iodine and palladium with additional set of polarization and diffuse functions taken from the aug-cc-pVTZ-PP basis set, whereas for other elements the 6-311++G(3df, 3pd) basis set has been used.

The calculations were performed using the Gaussian09 suite, while the molecular geometries were edited in the Molden 5.0 and ArgusLab 4.0.1 codes. The figures were created using the Inkscape 0.91 and CylView programs.

3 Results and Discussion

3.1 Trifluoroethylation of indoles [1]

The introduction of fluorine containing functional groups into molecules can improve their pharmaceutical properties. Our experimental partners developed a synthetic method for a C3-selective 2,2,2-trifluoroethylation method for a large set of indole substrates.



Base	Yield of 3	3:4 ratio
-	70 %	2:1
DTBPy	84 %	1:0

Scheme 1: The investigated reaction.

Our conclusions on the reaction mechanism can be summarized as follows:

- the rate-determining step is the C–C bond formation resulting in a σ-complex,
- the role of the applied base is the deprotonation of this σ-complex,
- the base can also be subject of an N-alkylation, therefore it competes with the C-alkylation of the substrate
- the barrier heights of the C-alkylations can be tuned varying the substituents of the indole frame,
- the barrier height differences of the competing C- and N-arylations determine the efficiency of the transformation towards the desired C-alkylated indole.
- with appropriately chosen base–substrate pairs the reaction can result in efficient C-alkylation

3.2 N-arylation of heterocycles [2]

Our experimental partners have developed an efficient N-arylation method for pyrazoles, applying an organic-aqueous solvent mixture and ammonia base under catalyst-free conditions. We have investigated several different reaction paths suggesting a plausible mechanism. On the basis of the reaction mechanism we have successfully predicted the outcome of several N-arylations of other heterocyles.

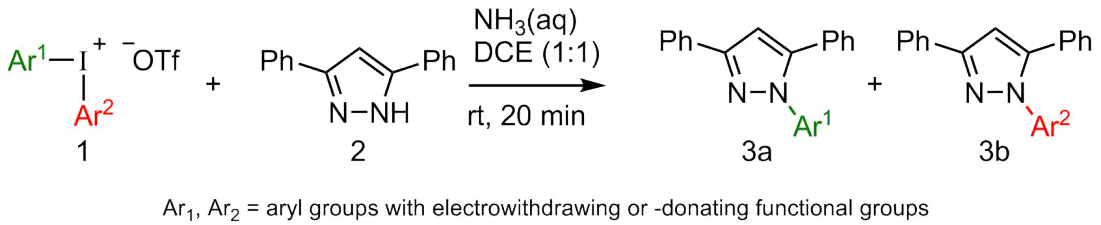


Figure 2: The investigated N-arylation reaction of 3,5-diphenylpyrazole with unsymmetric iodonium salts.

The results of this study can be summarized in these points:

- the initial formation of the iodonium–pyrazole adduct is followed by a subsequent deprotonation
- the presence of water is crucial as the transfer of the ionic byproduct is highly exergonic
- the rate-determining step is the N-arylation of the deprotonated complex
- the reaction is under kinetic control, as the selectivity is determined by the activation barrier difference between the two possible arylations
- we have validated this theory by constructing a new variable (product excess, $pe = 100\frac{c_1-c_2}{c_1+c_2} = 100\frac{\exp\left(\frac{\Delta\Delta G^{\ddagger}}{RT}\right)-1}{\exp\left(\frac{\Delta\Delta G^{\ddagger}}{RT}\right)+1}$) and comparing our theoretically predicted product ratios with the experimentally observed product ratios
- we have shown that the strategically positioned Lewis basic and Brønsted acidic centers in sufficient proximity enable the fast and efficient functionalization
- the mechanistic pattern is general, it can be applied in widering the scope of this N-arylation method
- we have selected various N-heterocyles and successfully predicted the outcome of the reaction.

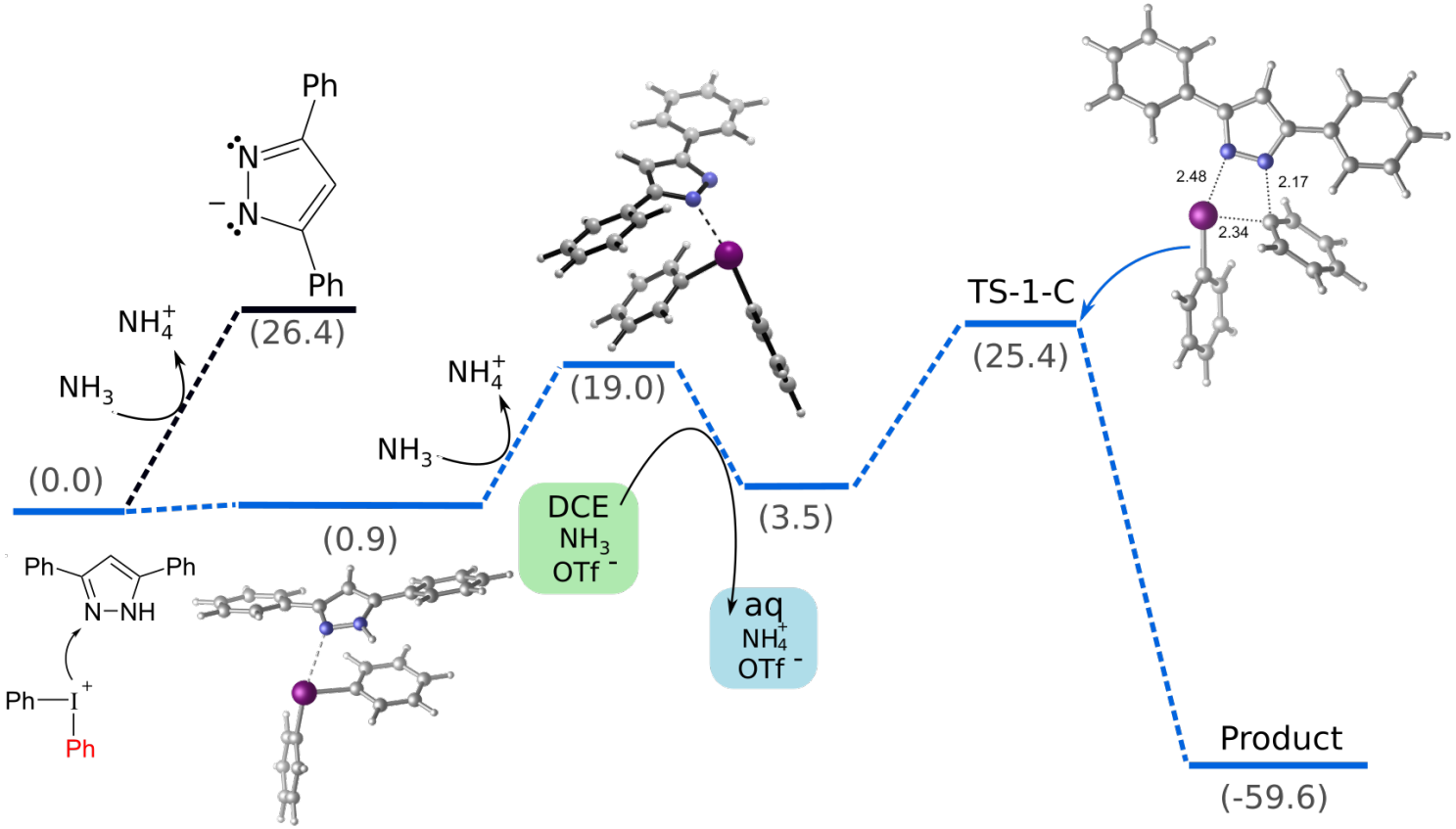


Figure 3: Free energy profiles for path C. Solvent corrected Gibbs free energy differences are in parentheses. Black curve: direct deprotonation of the 3,5-diphenylpyrazole. Blue curve: adduct formation and subsequent deprotonation, NH_4-triflate transfer to water and aryl group migration. Values are in kcal/mol.

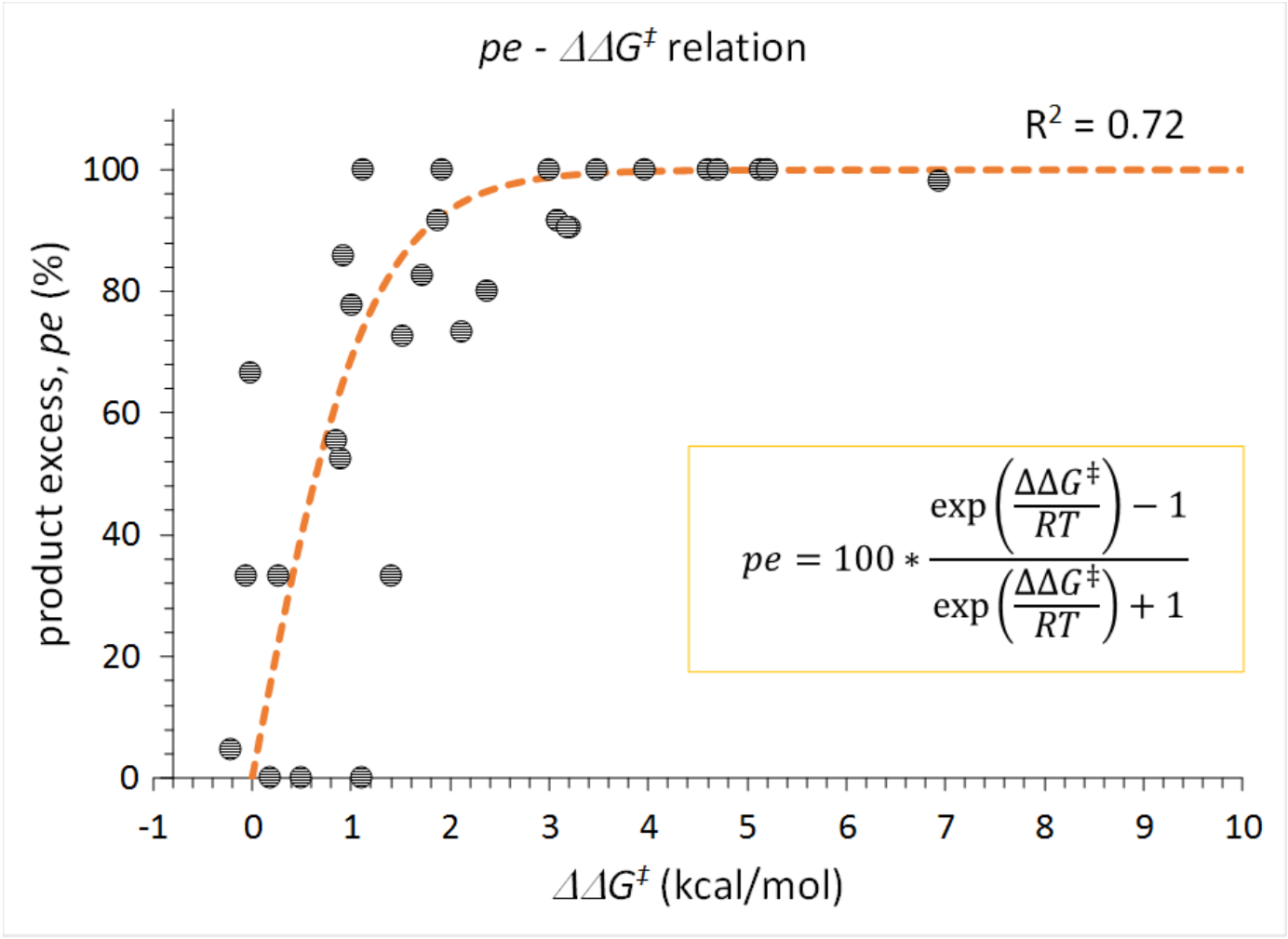
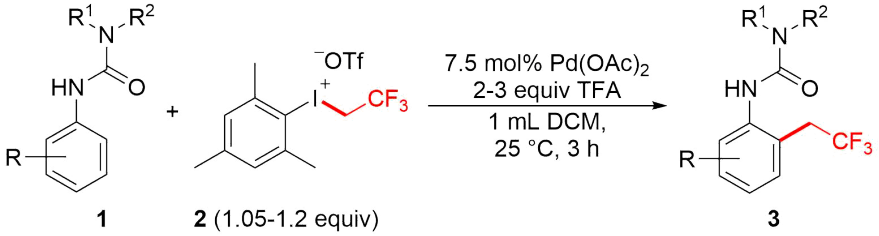


Figure 4: Relation of the experimental *pe* and theoretical $\Delta\Delta G^{\ddagger}$. The grey circles indicate the original data pairs, the dashed line shows the curve of the derived function.

3.3 Palladium catalyzed ortho-alkylation of aromatic ureas [3]

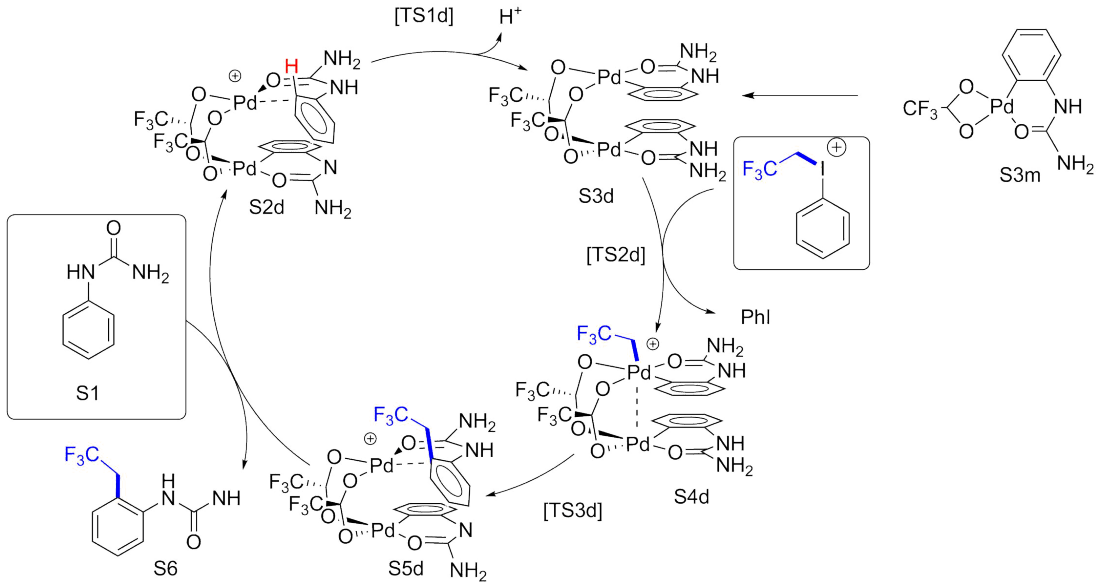
Iodonium salts are appropriate aryl and alkyl sources under catalytic conditions as well, but alkylation of aromatic rings is an underdeveloped field. Our synthetic partners have developed a direct, *ortho*-selective, late-stage installation of CF_3CH_2-group into aromatic ureas, and we have investigated the mechanism of this reaction in terms of catalytic cycles.



Scheme 5: The procedure for the direct *ortho*-trifluoroethylation of aromatic ureas.

Our findings can be summarized as follows:

- the trifluoroacetate salt is the active form of the Pd(II)-catalyst
- the bimetallic route is favorable due to the exergonic formation of the bimetallic complex **S3d**
- the rate determining step is the oxidative addition of the trifluoroethyl group to the palladium
- during the carbopalladation an outer-sphere deprotonation occurs, the proton is abstracted by a triflate anion directly
- the suggested scheme postulates a Pd(II)/Pd(IV) catalytic cycle



Scheme 6: Proposed dimeric route for the catalytic process.

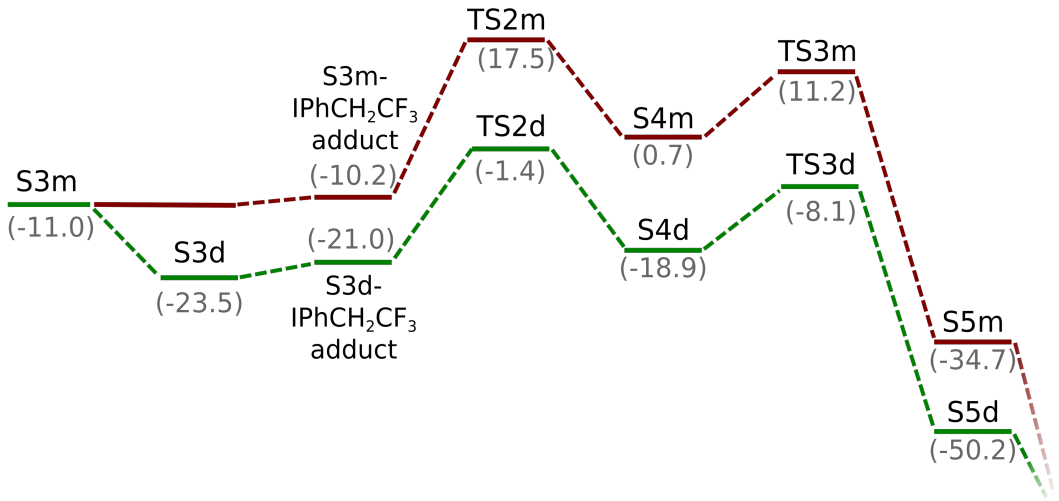
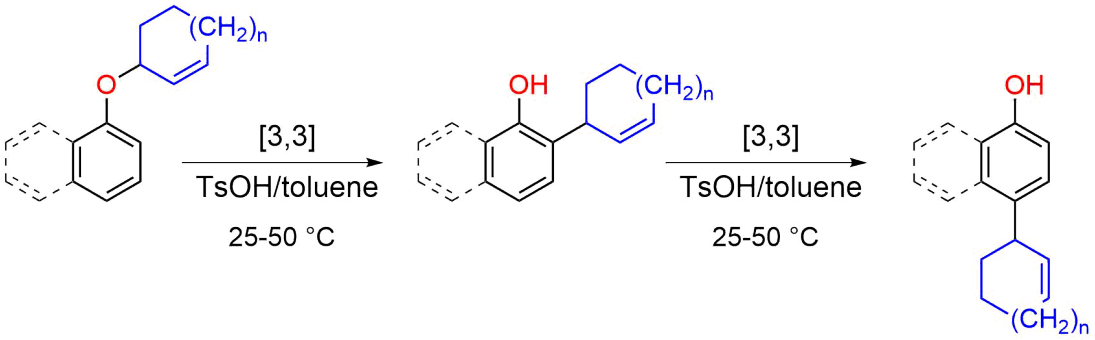


Figure 7: Gibbs free energy profiles for the trifluoroethylation steps along the monomeric and the dimeric route. Values are in kcal/mol.

3.4 Computational studies on the rearrangements of cycloalkenyl phenol derivatives [4]

Pericylic reactions e.g. sigmatropic rearrangements are well-known synthetic transformations in organic chemistry. The main feature of these reactions is that the transition state has a cyclic geometry with concerted bond breaking and formation steps. The mechanism of the acid catalyzed rearrangement of 2-cylcoalkenyl phenols was investigated in this project.



Scheme 8: Rearrangements of cycloalkenyl-aryl-ethers in the present project.

Our mechanistic proposal and further findings can be summarized as follows:

- the strong acidic environment implies that all reactants are in protonated form
- the bond breaking step leads to the formation of a peculiar intermediate, which is stabilized by the aromatic system of the phenol
- the formation of the intermediate is the rate-determining step
- based on the slight exergonicity the 2- and 4-substituted products are in equilibrium
- we have demonstrated with two-dimensional PES exploration that the anticipated one-step rearrangement would require higher energy
- this *pseudo*-Cope rearrangement cannot take place in the case of quinolines due to the high stability of the *N*-protonated form

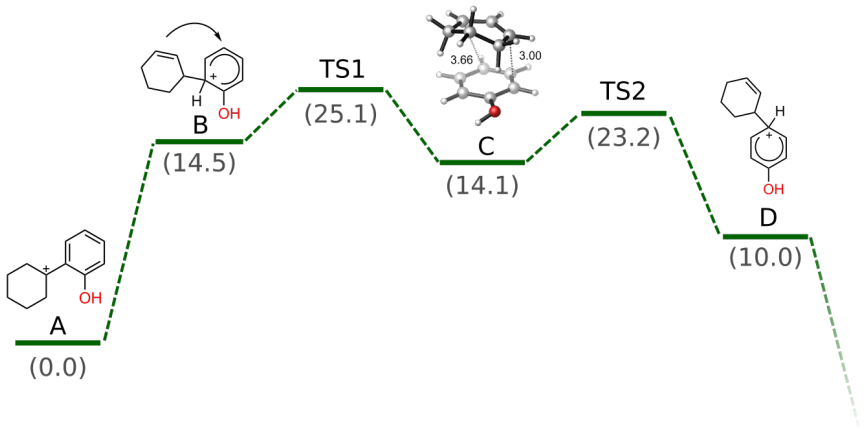


Figure 9: Free energy profile for the rearrangement of the cyclohexenyl shift. The profile shows a *pseudo*-Cope scheme, the values are in kcal/mol.

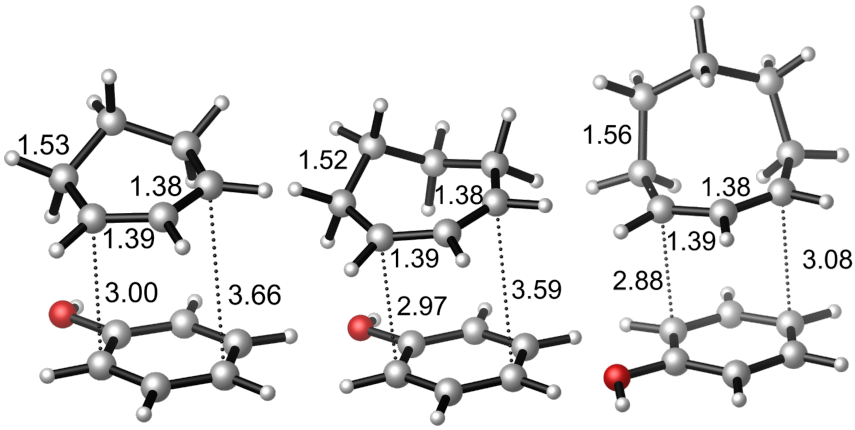


Figure 10: Structure of the intermediates. The displayed numbers are distances in Å.

4 Publications forming the basis of the thesis

[1] Tolnai G. L., Székely A., Makó Z., Gáti T., Daru J., **Bihari T.**, Stirling A., & Novák, Z.; Efficient direct 2,2,2-trifluoroethylation of indoles via C-H functionalization. *Chem. Commun.,* **2015,** *51(21),* 4488-4491.

[2] **Bihari T.**, Babinszki B., Gonda Zs., Kovács Sz., Novák Z., & Stirling, A.; Understanding and Exploitation of Neighboring Heteroatom Effect for the Mild N-Arylation of Heterocycles with Diaryliodonium Salts under Aqueous Conditions: A Theoretical and Experimental Mechanistic Study. *J. Org. Chem.,* **2016,** *81(13),* 5417-5422.

[3] Kovács Sz., Tóth B. L., Borsik G., **Bihari T.**, May V. N., Stirling A., & Novák Z.; Direct ortho-Trifluoroethylation of Aromatic Ureas by Palladium Catalyzed C-H activation: A Missing Piece of Aromatic Substitutions. *Adv. Synth. Catal.,* **2017,** *359,* 527-532.

[4] Törincsi M., Nagy M., **Bihari T.,** Stirling A., Kolonits P., & Novák, L.; Rearrangements of Cycloalkenyl Aryl Ethers. *Molecules,* **2016,** *21(4),* 503-516.